Agenda

- Excipients: Importance & risk
- Regulatory policies
- Warning letter details & outcomes

1 Excipients: Importance and risk

Why excipients matter

- **Excipients** are all ingredients in a drug product other than the active pharmaceutical ingredient (API)

  - They can comprise 90% or more of a drug product's volume
  - Excipients have many functions, including lubrication, flavoring, buffering, and often help ensure the API is delivered to the site of action

- Complex non-transparent supply chains for excipients can lead to economically motivated or accidental adulteration

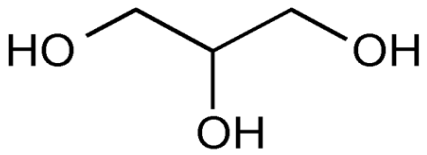
History of diethylene glycol contamination in excipients

Country	Year	Incident
USA	1937	Sulfanilamide Elixir formulated with DEG – 107 deaths *Resulted in the enactment of the1938 FFD&C Act*
South Africa	1969	Sedative formulated with DEG – 7 deaths
India	1986	Medicinal glycerin laced with DEG – 14 deaths
Nigeria	1990	Acetaminophen syrup containing DEG – 40 deaths (some sources say 200 deaths)
Bangladesh	1990-2	Acetaminophen syrup containing DEG – 339 deaths
Haiti	1995/6	Cough medicine containing DEG – 85 deaths
Nigeria	2008/9	Propylene glycol in teething formula contaminated with DEG – 84 deaths
Bangladesh	2009	Children's paracetamol syrup to adulterated with DEG – 24 children reported dead
India	2020	Propylene glycol in cough syrup contaminated with DEG – nine children reported dead from renal failure

2016 USP Glycerin Monograph

Official Name or Title: USP Glycerin

$C_3H_8O_3$ 92.09
1,2,3-Propanetriol;
Glycerol [56-81-5].



DEFINITION

Glycerin contains NLT 99.0% and NMT 101.0% of $C_3H_8O_3$, calculated on the anhydrous basis.

IDENTIFICATION

[NOTE—Compliance is determined by meeting the requirements for *Identification* tests *A*, *B*, and *C*.]

- **A.** INFRARED ABSORPTION ⟨197F⟩
- **B.** LIMIT OF DIETHYLENE GLYCOL AND ETHYLENE GLYCOL

  Acceptance criteria: If a peak at the retention times for the diethylene glycol or ethylene glycol is present in the *Sample solution*, the peak response ratio relative to 2,2,2-trichloroethanol is NMT the peak response ratio for diethylene glycol or ethylene glycol relative to 2,2,2-trichloroethanol in the *Standard solution*; NMT 0.10% each for diethylene glycol and ethylene glycol is found.
- **C.** Examine the chromatograms obtained in *Identification* test *B*. The retention time of the glycerin peak of the *Sample solution* corresponds to that obtained in the *Standard solution*.

Organic Impurities

- **PROCEDURE 1: RELATED COMPOUNDS**

  Acceptance criteria

  Individual impurities: NMT 0.1%

  Total impurities: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **USP REFERENCE STANDARDS** ⟨11⟩

  USP Diethylene Glycol RS
  USP Ethylene Glycol RS
  USP Glycerin RS
  1,2,3-Propanetriol.
  $C_3H_8O_3$ 92.10

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Example regulatory policies: US & China

US Law: 21 CFR 211.84(d)(1) & (2)

d. Samples shall be examined and tested as follows:

1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

China: Pharmaceutical Administration Law 2019

第四十五条　生产药品所需的原料、辅料，应当符合药用要求、药品生产质量管理规范的有关要求。

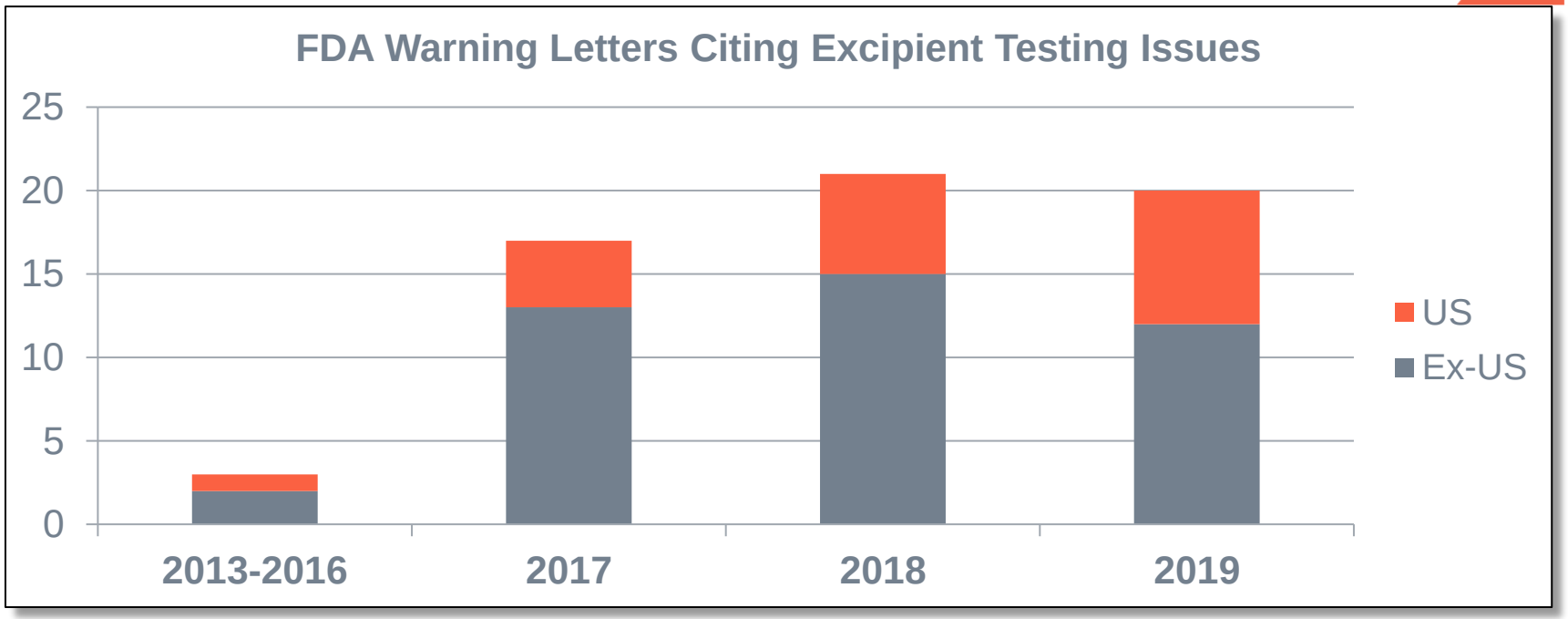
生产药品，应当按照规定对供应原料、辅料等的供应商进行审核，保证购进、使用的原料、辅料等符合前款规定要求。

- Article 45 :The API and excipients needed for the production of drugs shall meet the requirements for medicinal use and the relevant requirements of the quality control standards for the production of drugs.
  - In the production of pharmaceuticals, suppliers supplying API and excipients **shall be audited in accordance with the regulations** to ensure that API and excipients purchased and used conform to the requirements of the preceding paragraph.

[Emphasis added]

3 FDA warning letter details & outcomes

FDA warning letters citing excipient testing issues



Sharp increase in warning letters citing **lack of excipient ID testing** of every incoming lot and/or **over-reliance on supplier COA** for attribute testing

CDER Warning Letter 320-18-48,Sihor, India, April 24/18

1. **Your firm failed to ensure the identity of components, including your active ingredients and excipients from various suppliers (21 CFR 211.84(d)(1) and (2)).**

"You failed to test incoming components you use in manufacturing drug products to determine their conformance to identity, purity, strength, and other appropriate specifications. Your firm released components for use in drug product manufacturing based on certificates of analysis (COA) from your supplier without establishing the reliability of the suppliers' analyses through appropriate validation. **For example, your firm did not test each lot of glycerin used as a component of your drugs to determine whether diethylene glycol (DEG) or ethylene glycol (EG) was present.** Because you did not test each glycerin lot using the USP identification test that detects these hazardous impurities, you failed to assure the acceptability of lots used in drug product manufacture. **DEG contamination in pharmaceuticals has resulted in various lethal poisoning incidents in humans worldwide**."

[Emphasis added]

CDER Warning Letter 320-18-60, Foshan City, China, June 26/18

"2. Your firm failed to conduct at least one test to verify the **identity of each component** of a drug product. Your firm also failed to establish the **reliability of component supplier analyses** on which you rely in lieu of certain tests through appropriate validation of supplier's test results at appropriate intervals (21 CFR 211.84(d)(1) and (2))."

"Instead, your firm relied on certificates of analysis (COA) from unqualified suppliers."

[Emphasis added]

CDER Warning Letter 320-18-52, County Offaly, Ireland, May 16/18

In response to the warning letter, FDA instructed the firm to:

• "Provide written procedures for how you will **qualify your suppliers, both initially and on an ongoing basis**. Describe whether you **intend to test each lot of incoming components for all attributes.** Alternatively, if you intend to rely on the supplier's certificate of analysis, provide specifics on how you will **verify each suppliers' test results at regular intervals and include a commitment to test every incoming component lot for identity, at minimum.**

• "Provide a **comprehensive, independent review of your laboratory practices, methods, equipment and analyst competencies.** Based on this review, provide a detailed corrective action and preventative action plan to **fully remediate your laboratory system**."

• "**Provide a detailed risk assessment for drug products that contain glycerin and are within expiry in the U.S. market. Test retain samples of all lots for DEG and EG. If** you find that you released any batch for which results are out-of-specification, indicate the **corrective actions you will take,** such as customer notifications and **product recalls**.

[Emphasis added]

Examples of Warning Letter Outcomes

"Failure to promptly correct these violations may result in **legal action without further notice** including, without limitation, **seizure and** ." *CMS# 552896*

"FDA placed your firm on I
320-18-48

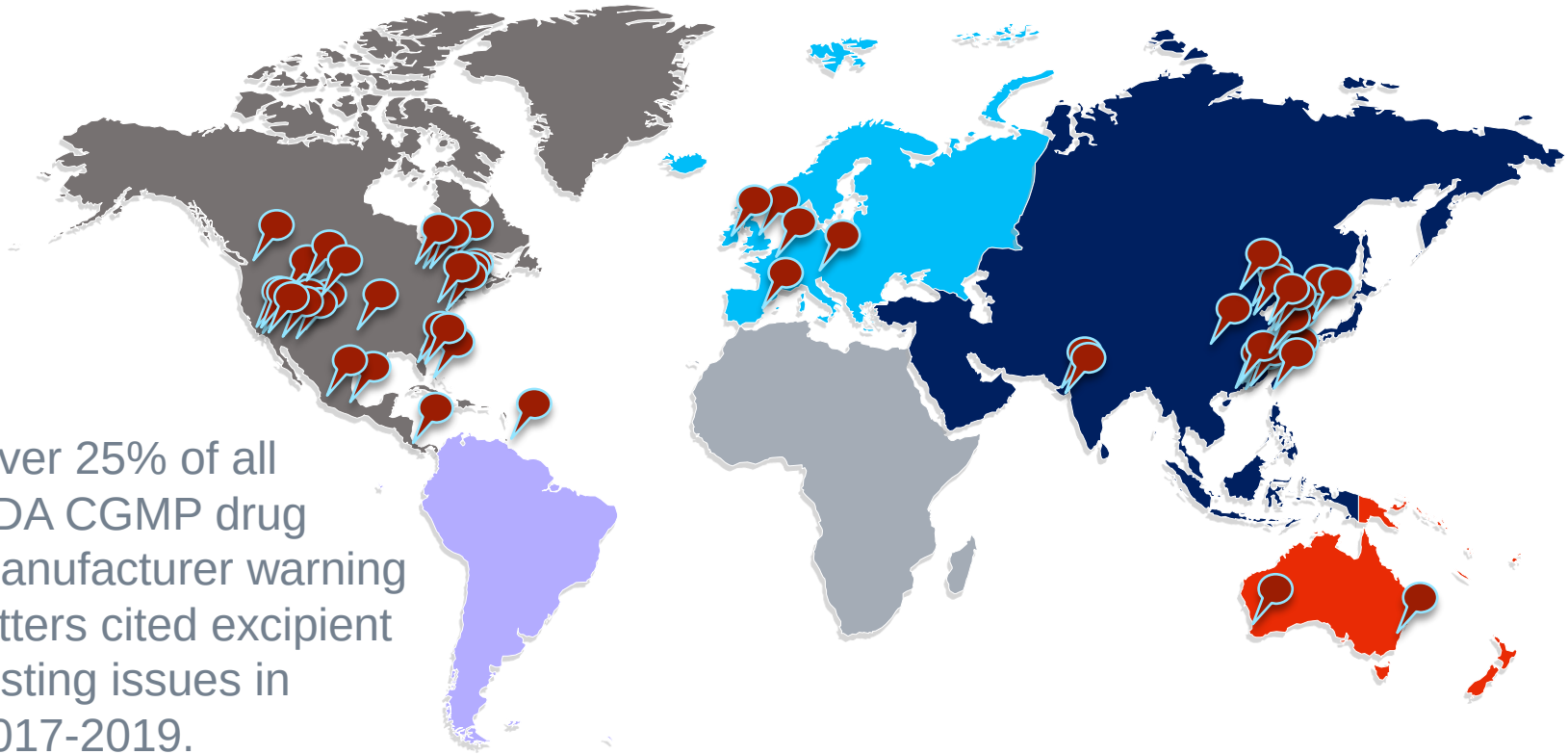
"FDA placed your firm on Import Alert 66-40 on March 8, 2018."
320-18-54

0 on March 5, 2018."

Note:
You and your customer, (b)(4), have a quality agreement regarding the manufacture of (b)(4) Cream. **You are responsible** for the quality of drugs you produce as a contract facility, regardless of agreements in place with product owners.
320-18-54

[Emphasis added]

58 FDA Warning Letters in 2017-19 citing reliance on COA and/or lack of identity testing of incoming excipients



Over 25% of all FDA CGMP drug manufacturer warning letters cited excipient testing issues in 2017-2019.


What will you do to ensure the quality of medicines in the future?

Thank You

Empowering a healthy tomorrow